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Abstract: Background: The risk of adverse events in patients with left ventricular non-compaction cardiomyopathy (LVNC) is substantial. This study was designed to determine the prognostic value of NT-proBNP, left ventricular ejection fraction (LVEF), NYHA class, and exercise capacity in LVNC patients. Methods: Cox regression analyses were performed for evaluating the prognostic value of NT-proBNP, LVEF, NYHA class, and exercise capacity on the occurrence of death or heart transplantation. 153 patients were included. Results: During 1013 person-years (longest follow-up 18.5 years) 23 patients (15%) died or underwent heart transplantation. We observed a significant relationship of NT-proBNP (adjusted HR 2.44, 95% CI 1.45–4.09, for every NT-proBNP doubling, p = 0.0007) and LVEF (adjusted HR for age 60 years: 2.68, 95% CI 1.62–4.41, p = 0.0001) with the risk of death or heart transplantation. Combined covariate analysis indicated a strong influence of NT-proBNP (adjusted 2.89, 95% CI 1.33–6.26, p = 0.007), whereas LVEF was no longer significant (adjusted HR 0.82, 95% CI 0.42–1.67, p = 0.66) demonstrating a favorable prognostic power of NT-proBNP over LVEF. An increase in NYHA class was associated with a worse outcome, and exercise capacity revealed a trend in the same direction. For all the abovementioned analyses, similar results were obtained when assessing the values at first presentation. Conclusion: This study provides evidence that an increase in NT-proBNP is a strong predictor of outcome in patients with LVNC. The prognostic power of NT-proBNP is at least as good as that of LVEF, indicating that routine NT-proBNP measurement may improve risk assessment in LVNC.

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Prognostic power of NT-proBNP in left ventricular non-compaction cardiomyopathy

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Key words: NT-proBNP, natriuretic peptide, ejection fraction, prognosis, heart failure.

ABSTRACT

Background – The risk of adverse events in patients with left ventricular non-compaction cardiomyopathy (LVNC) is substantial. This study was designed to determine the prognostic value of NT-proBNP, left ventricular ejection fraction (LVEF), NYHA class, and exercise capacity in LVNC patients.

Methods – Cox regression analyses were performed for evaluating the prognostic value of NT-proBNP, LVEF, NYHA class, and exercise capacity on the occurrence of death or heart transplantation. 153 patients were included.

Results – During 1013 person-years (longest follow-up 18.5 years) 23 patients (15%) died or underwent heart transplantation. We observed a significant relationship of NT-proBNP (adjusted HR 2.44, 95%-CI 1.45-4.09, for every NT-proBNP doubling, p = 0.0007) and LVEF (adjusted HR for age 60 years: 2.68, 95%-CI 1.62-4.41, p = 0.0001) with the risk of death or heart transplantation. Combined covariate analysis indicated a strong influence of NT-proBNP (adjusted 2.89, 95%-CI 1.33-6.26, p = 0.007), whereas LVEF was no longer significant (adjusted HR 0.82, 95%-CI 0.42-1.67, p = 0.66) demonstrating a favorable prognostic power of NT-proBNP over LVEF. An increase in NYHA class was associated with a worse outcome, and exercise capacity revealed a trend in the same direction. For all the above mentioned analyses, similar results were obtained when assessing the values at first presentation.

Conclusion – This study provides evidence that an increase in NT-proBNP is a strong predictor of outcome in patients with LVNC. The prognostic power of NT-proBNP is at least as good as that of LVEF, indicating that routine NT-proBNP measurement may improve risk assessment in LVNC.

INTRODUCTION

Left ventricular non-compaction cardiomyopathy (LVNC) is a distinct primary cardiomyopathy characterized by a thin, compacted, outer (epicardial) layer and a thick, non-compacted, inner (endocardial) layer with deep recesses between prominent trabeculations(1-3). Since its first description, the awareness of LVNC has increased (4, 5). With wider recognition of the disease and systematic family screening the number of asymptomatic patients diagnosed with LVNC is increasing. Symptomatic patients typically present with heart failure, ventricular arrhythmias or thromboembolic events (6-8). However, overall event rates and predictors of outcome remain ill defined. Mortality rates in earlier studies range from 2% to 35%, over median follow-up periods ranging from 2.3 to 4.5-years (9-13). These studies observed an association between presentation with symptoms, reduced left ventricular ejection fraction and the risk for adverse outcomes (7, 8, 10-12). Nevertheless, quantitative data allowing a reliable assessment of a patient's risk is scarce.

In cardiomyopathies other than LVNC, parameters like left ventricular ejection fraction, heart failure symptoms, and exercise capacity correlate with clinical outcome. Due to its low prevalence, the value of such parameters in LVNC is not as well defined, and the prognostic relevance of the heart failure marker N-terminal fragment of prohormone brain natriuretic peptide (NT-proBNP) as well as that of exercise capacity have not been examined so far.

The aim of this study was to determine the prognostic value of NT-proBNP in LVNC patients per se and in comparison with left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, and exercise capacity. In addition, clinically established cut-off values (LVEF 55% and LVEF 30%, specified standard values for NT-proBNP) as well as cut-off points providing the best

prognostic discrimination in regard to death and heart transplantation were assessed.

METHODS

Patients

All patients diagnosed with isolated LVNC between 1988 and 2015, identified from the clinical and imaging databases at the University Hospitals Zurich and Basel were included in this retrospective analysis. The study was approved by the local ethical committees of Zurich and Basel and informed consent was obtained. The echocardiographic criteria described by Jenni et al. were applied to establish the diagnosis (14). These criteria include 1) a thickened, two-layered myocardium with a compacted outer and a non-compacted inner layer, ratio of systolic thickness of non-compacted to compacted layer > 2 in parasternal short axis view, 2) color Doppler evidence of deep intertrabecular recesses filled with blood from the left ventricular cavity, 3) typical distribution of affected segments in the mid-lateral, mid-inferior and apical left ventricle, and 4) absence of coexisting cardiac abnormalities for the isolated form of the disease.

Demographical, clinical, and technical (laboratory, exercise test, echocardiography) data were collected retrospectively and entered into a web-based database (SecuTrial, Berlin, Germany) hosted by the Clinical Trial Center at the University of Zurich.

The endpoint was defined as the occurrence of all-cause death or need for heart transplantation as assessed in hospital records as well as by telephone survey.

Prohormone Brain Natriuretic Peptide

NT-proBNP levels were measured in heparinized blood plasma using the Cobas Analyzer (Roche Diagnostics, Basel, Switzerland) at the Institutes of Clinical Chemistry of the University Hospital Zurich and University Hospital Basel. Normal NT-proBNP values were defined as follows: for males <60 years, ≤100 ng/l; for

males ≥60 years, ≤172 ng/l; for females <60 years, ≤164 ng/l; and for females ≥60 years, ≤225 ng/l (15).

Left Ventricular Ejection Fraction

Echocardiography studies were performed using commercially available equipment (iE33 or Epiq 7, Philips Medical Systems, Andover MA, USA; Vivid7 or E9, GE Healthcare, Buckinghamshire, UK; Acuson Sequoia 512, Siemens Medical Solutions, Forchheim, Germany). LVEF was determined by the biplane Simpson's method.

NYHA Functional Class

NYHA functional class data was collected via medical history and assessed as previously described (16).

Exercise capacity

Exercise capacity was determined by bicycle ergometer (Schiller, Switzerland) using an individualized ramp protocol and expressed as percent of target performance (PoTP). Target performance (Watt) was defined as follows: for males, 6.773 + (136.141 × BSA) – (0.064 × age) – (0.916 × BSA × age); for females, 3.933 + (86.641 × BSA) – (0.015 × age) – (0.346 × BSA × age) (17). BSA (m^2) was determined as follows: 0.007184 × weight (kg)^0.425 × height (cm)^0.725.

Statistical analysis

Statistical analysis of the time-to-event data was performed using Cox proportional hazard models with age as time scale (with or without adjustment for specific variables as stated in the results part), so patients were treated as left-truncated at

their age of entry. In order to check for non-informative late entry, the age at entry of a patient was included in the adjusted models, without showing a significant effect (18). Time-dependent variation of the covariates LVEF, NT-proBNP, NYHA class, and PoTP was taken into account by creating a data set listing the time-dependent covariates for each follow-up visit of a patient and the time span during which the values of the covariates did not change (19). In case of violation of the proportional hazards assumption, examined by plotting the scaled Schoenfeld residuals against time (age of patients) and by applying the test developed by Grambsch and Therneau (20), the covariate was modeled using a time-dependent coefficient (linear time scale), and hazard ratios were assessed for different ages separately. Entry into study was defined as the first visit in one of the two study hospitals when at least one parameter was recorded; end of data acquisition for the study was 19.04.2015 (retrieval of data set).

To determine a cut-off value, we used the minimum p-value approach (21), i.e., we fitted a Cox regression model at each observation of a restricted set of all potential cut points. Using the p-value of the group comparison (above and below the cut point) as selection criterion, the cut point resulting in the smallest p-value was taken. The p-value, the estimated log-hazard ratio (HR) and its standard error were corrected for multiple testing (22). In the analysis of different cut-offs, we considered a minimum of two events per group necessary to avoid complete separation, i.e., a split where all events are exclusively in one group. NT-proBNP values were transformed by taking the binary logarithm in order to attain a symmetric distribution. As statistical software, we used the R programming language.

RESULTS

Patients

During 1013 person-years (longest follow-up 18.5 years) 23 patients (15%) died or underwent heart transplantation. An overview of the study population, patient groups, measurements, follow-up, and outcome is provided in Table 1.

Prohormone Brain Natriuretic Peptide

The median NT-proBNP level in all non-event associated measurements (all values except event-preceding values) was 292 ng/l. Median NT-proBNP level at the last measurement preceding an event was 6416 ng/l (Figure 1A).

Cox regression revealed a highly significant relationship between NT-proBNP level (log2 transformed) and the risk of death or heart transplantation. This dependency was observed both in the unadjusted analysis (HR 2.37, 95%-CI 1.49-3.76, p=0.0003) and after adjustment for age and gender (adjusted HR 2.44, 95%-CI 1.45-4.09, p = 0.0007, Figure 1C).

Next, the prognostic values of normal NT-proBNP levels, NT-proBNP levels above 2000 ng/l, and NT-proBNP levels above 10000 ng/l were assessed. No event was recorded in patients with NT-proBNP levels in the normal range indicating an excellent prognosis for these patients (Figure 1D). In contrast, NT-proBNP levels higher than 2000 ng/l were associated with a very poor prognosis. This threshold provided the best prognostic discrimination with a hazard ratio of 40.2 adjusted for age and gender (95%-CI 5.57-289, p <0.0001, Figure 1D) with respect to death or heart transplantation using Cox regression models and the minimum p-value method. NT-proBNP levels of more than 10000 ng/l were associated with an adjusted hazard ratio of 14.8 (95%-CI 1.75-125.31, p=0.003).

Table 1: Overview of patient groups, measurements, and follow-up

	All patients	NT-proBNP	LVEF	NYHA	PoTP
Number of patients	153	87	148	105	86
Number of measurements	1462	290	535	437	200
Age at entry (years; mean ±SD)	43 ±19.4	47 ±17.5	43 ±19.1	43 ±19.0	42 ±16.7
Male sex (%)	91 (59.5)	56 (64.4)	87 (58.8)	69 (65.7)	58 (67.4)
Follow-up (days; median, IQR)	2193 (888-3721)	1775 (1015-2861)	3264 (1447-4280)	3057 (1199-4209)	2320 (934-3828)
Death (%)	15 (9.9)	11 (12.6)	15 (10.1)	12 (11.4)	7 (8.1)
Heart transplantation (%)	8 (5.2)	4 (4.6)	7 (4.7)	5 (4.8)	4 (4.7)
Death or heart transplantation (%)	23 (15.1)	15 (17.2)	22 (14.8)	17 (16.2)	11 (12.8)
Age at endpoint (years; mean ±SD)	63 ±16.2	61 ±17.2	63 ±16.3	61 ±17.3	55 ±15.9

Number of patients in which specific parameters were assessed, and number of measurements per parameter. Follow-up duration, number of deaths and heart transplantations, and age at time of death or heart transplantation for each group of patients in which a specific parameter was assessed. NT-proBNP = N-terminal fragment of prohormone brain natriuretic peptide; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; PoTP = percent of target performance.

To assess the prognostic value of NT-proBNP levels at initial presentation, we performed a Cox regression analysis including only the values at first presentation as covariates. HRs of initial NT-proBNP levels with respect to death or heart transplantation were as follows: unadjusted HR 1.8, 95%-CI 1.46-2.22, p<0.0001; adjusted for age and gender HR 1.69, 95%-CI 1.35-2.10, p<0.0001.

Left Ventricular Ejection Fraction

Median LVEF in all non-event related measurements was 45%. Median LVEF at the last measurement before an event was 21% (Figure 1B).

A Cox regression analysis revealed a highly significant relationship between decrease in LVEF and the risk of death or heart transplantation. Allowing for a time-dependent effect of LVEF, the HR is decreasing with age, adjusted for age at study entry and gender (age 30 years: HR 6.14 for every 10% decrease, 95%-CI 1.84-20.59, p = 0.003; age 40 years: HR 4.68, 95%-CI 1.82-12.00, p = 0.001; age 50 years: HR 3.51, 95%-CI 1.76-7.10, p = 0.0004; age 60 years: HR 2.68, 95%-CI 1.62-4.41, p = 0.0001; age 70 years: HR 2.02, 95%-CI 1.33-3.07, p = 0.001; Figure 1C) and unadjusted (supplemental material).

The prognostic value of an LVEF >55% or <30%, respectively, was also assessed. Only one event was recorded in patients with an LVEF >55%, indicating an excellent prognosis for this patient group. In contrast, an LVEF <30% was associated with a hazard ratio of 8.52 adjusted for age and gender (95%-CI 2.82-25.75, p<0.0001, Figure 1D). An LVEF of 15% provided the best prognostic discrimination (HR adjusted for age and gender 12.58, 95%-CI 3.51-45.1, p<0.0001, Figure 1D) using Cox regression models and the minimum p-value method, indicating a very poor prognosis for patients with an LVEF below this value.

To assess the prognostic value of LVEF at initial presentation, we performed a Cox regression analysis including the values at first presentation only. This analysis provided similar results as the analysis using time-dependent covariates. Hazard ratios of initial LVEF (per 10% decrease) were as follows: unadjusted HR 2.07, 95%-CI 1.50-2.87, p <0.0001; HR adjusted for age and gender 1.67, 95%-CI 1.11-2.30, p = 0.007.

Combined Covariate Analysis of NT-proBNP and LVEF

Bivariate analysis of the linear relationship of NT-proBNP (log2 transformed) and LVEF revealed a moderate to strong negative correlation (Pearson's r = -0.68, Figure 2A). Similar results were obtained after the data had been weighted with weights equal to the time span during which the values of both covariates did not change (weighted r = -0.59, Figure 2B).

To compare the prognostic value of NT-proBNP to that of LVEF, a Cox regression model was fitted using NT-proBNP and LVEF as covariates. NT-proBNP exhibited a very strong influence on the risk of death or heart transplantation (HR 2.69, 95%-CI 1.34-5.41, p = 0.005), whereas LVEF did no longer seem to be related (HR 0.82, 95%-CI 0.42-1.67, p = 0.67, Figure 2C) indicating collinearity of the two parameters with favorable prognostic power of NT-proBNP over LVEF. A similar effect was observed after adjustment for age at study entry (NT-proBNP: adjusted HR 2.89, 95%-CI 1.33-6.26, p = 0.007; LVEF: adjusted HR 0.82, 95%-CI 0.42-1.67, p = 0.66).

To compare the prognostic value of NT-proBNP and LVEF at initial presentation, we also performed an analysis using only the initial values of NT-proBNP and LVEF as covariates. Initial NT-proBNP level exhibited a strong impact on the risk of death or heart transplantation (HR 1.69, 95%-CI 1.27-2.24, p =

0.0003), whereas LVEF was no longer related (HR 1.22 95%-CI 0.68-2.30, p = 0.50), indicating that the initial values also exhibit collinearity with favorable prognostic power of NT-proBNP over LVEF. After adjustment for age at study entry, however, there was no evidence for a difference in prognostic power between the two parameters.

NYHA Functional Class

Among all the non-event related measurements, 12.3% were in NYHA class III or IV (NYHA classes III and IV merged due to only a single patient in NYHA class IV). At the last assessment preceding an event, 29.4% of patients were in NYHA class III or IV (Figure 3A).

An increase in NYHA class was associated with a worse outcome, both unadjusted (HR 3.48, 95%-CI 1.57-7.75, p = 0.002) and adjusted for age and gender (HR 3.58, 95%-CI 1.57-8.15, p = 0.002, Figure 1C). Comparing the different NYHA classes among each other revealed the following adjusted hazard ratios: NYHA III/IV vs. NYHA I: HR 12.05, 95%-CI 2.04-71.32, p = 0.006; NYHA III/IV vs. NYHA II: HR 3.05, 95%-CI 0.87-10.71, p = 0.082; NYHA II vs. NYHA I: HR 3.95, 95%-CI 0.80-19.49, p = 0.091. There were no classes without an event (NYHA class I, 2 events; NYHA class II, 10 events; NYHA class III/IV, 5 events).

Exercise capacity

Median PoTP in all non-event related measurements was 89% (Figure 3B). The median PoTP at the last assessment before an event was 56%. A Cox model, adjusted for age at study entry and gender and allowing for a time-dependent effect of PoTP revealed for the age of 30, 40, and 50 years a significant relationship of decreasing PoTP and the risk of death or heart transplantation. There was no

evidence for such an association for the age of 60 and 70 years. Age 30 years: HR 12.15 for every 10% decrease, 95%-CI 1.65-45.27, p = 0.014; age 40 years: HR 5.65, 95%-CI 1.38-22.95, p = 0.016; age 50 years: HR 2.6, 95%-CI 1.14-5.93, p = 0.023; age 60 years: HR 1.20, 95%-CI 0.86-1.67, p = 0.28; age 70 years: HR 0.55, 95%-CI 0.33-0.92, p = 0.024 (Figure 1C). Unadjusted analysis revealed an analogous result (supplemental material).

Cox regression models and the minimum p-value method were used to determine the cut-off point with the best prognostic discrimination. A value of 56% provided the best discrimination for PoTP between patients with and without events (HR 6.679, 95%-CI 1.98-22.52, p = 0.003). PoTP at initial presentation was also assessed but did not generate additional prognostic information (unadjusted HR 0.99, p = 0.20; HR adjusted for age and gender 0.99, p = 0.51).

DISCUSSION

The predictors of mortality remain ill-defined in patients with LVNC. This study determined the prognostic value of NT-proBNP in comparison with other markers of left ventricular function such as LVEF, NYHA functional class, and exercise capacity in the largest LVNC cohort published to date, with 153 patients and a median follow-up duration of more than 6 years. The overall mortality and heart transplantation rate in our cohort was 15%, which is in the range of previous studies reporting rates between 2% and 35% (9-13).

Prognostic value of NT-proBNP and LVEF

NT-proBNP was an extremely strong marker of death or heart transplantation in LVNC patients. Not a single case of death or heart transplantation was recorded in patients with normal NT-proBNP levels, indicating an excellent prognosis in such individuals. In contrast, every doubling of NT-proBNP was associated with a 2.4-times higher and a NT-proBNP level >2000 ng/l with a 40-times higher risk, respectively, of death or heart transplantation. A higher cut-off value did not lead to additional prognostic power, suggesting that the manifestation of ventricular dysfunction and heart failure as such rather than the degree of congestion within the pathologic range is associated with a poor prognosis. This interpretation is consistent with the observation that LVNC patients with symptoms of heart failure have a worse prognosis when compared to asymptomatic patients (10). An association of elevated NT-proBNP levels and worse clinical outcome has been documented for dilated cardiomyopathy (23), hypertrophic cardiomyopathy (24), and hypertensive heart disease (25), indicating that the level of natriuretic peptide mainly reflects the degree of left ventricular dysfunction rather than representing a specific type of cardiomyopathy.

Similar to previous reports in smaller cohorts (7-12), LVNC patients exhibiting an impaired left ventricular systolic function were at higher risk of death or heart transplantation in this study. Only a single death (acute circulatory failure of unknown cause at the age of 84 years) occurred in the patient group with an LVEF ≥55%, indicating a very good prognosis in patients with an ejection fraction in the normal range. In contrast, every reduction of LVEF was associated with a significantly higher risk of death or heart transplantation. This effect was consistent amongst all ages with the strongest effect at young age. A possible reason for this observation is that older patients have more comorbidities which influence the risk of death irrespective of LVEF. Average age at death or heart transplantation was 63 years, thus the hazard ratio for the age 60 is presented in figure 1C. In line with previous observations (10), a similar impact of LVEF on mortality was observed when examining the values at initial presentation.

In a Cox regression model using both NT-proBNP and LVEF as covariates, NT-proBNP exhibited a very strong influence on the risk of death or heart transplantation whereas LVEF was not significant, indicating a favorable prognostic power of NT-proBNP over LVEF. This finding indicates that NT-proBNP may be more useful than LVEF for predicting outcome in LVNC. This superiority was observed in the time-dependent covariate analysis as well as in the unadjusted analysis of values at initial presentation. Hence, NT-proBNP is useful not only for risk assessment when the patient is seen for the first time but particularly during follow-up. Similar observations have been made in patients with congestive heart failure (26). The prognostic superiority of NT-proBNP over that of LVEF may result from the different profile of cardiovascular responses that the two parameters reflect; while LVEF represents left ventricular systolic impairment, NT-proBNP detects both left ventricular and right ventricular dysfunction as well as elevated pulmonary pressure (27). A conceivable

additional explanation is that NT-proBNP is a standardized laboratory parameter with very high accuracy (28), while echocardiographic assessment of LVEF is dependent on the investigator's experience and image quality, and its accuracy is an ongoing controversial debate (29).

Prognostic value of NYHA functional class and exercise capacity

An increase in NYHA functional class was associated with a 3.6-times increased risk of death or heart transplantation, both in a time-dependent covariate analysis and when examining the values at initial presentation, confirming findings from previous smaller LVNC studies (8, 10-12) and unselected heart failure patients (30) as well. This finding is of clinical interest since information on NYHA class is easily collected and can be monitored autonomously by the patient. However, in contrast to NT-proBNP, NYHA class is a subjective, semi-quantitative parameter with only 4 stages and is known to be much less specific than NT-proBNP for detecting congestive heart failure (31).

A decrease in exercise capacity measured as percentage of target performance was associated with a higher risk of death or heart transplantation for ages up to 50 years. The observed decrease of the effect with age could be due to the fact that PoTP is less frequently measured in this population and comorbidities influencing the risk of death are more common. In addition, PoTP does not only depend on cardiac function, but also on pulmonary function, the musculoskeletal system, and patient motivation. Peak oxygen consumption which was not available in most of the patients would possibly have been a more sensitive marker (32).

Study limitations

Even though the present study represents the largest LVNC cohort ever studied, it is still limited by the relatively small number of patients as compared to more common diseases, by the referral bias, and – given the observational retrospective study design – by a possible confounding bias as well as the problem of informative but missing measurements of patients not requiring medical care.

Conclusion

This study provides evidence that an increase in NT-proBNP is associated with a higher risk of death or heart transplantation in patients with LVNC. Furthermore, NT-proBNP is an extremely strong prognostic marker with a prognostic power at least as good as that of LVEF. This finding may have implications on the development of cost-effective risk assessment and treatment strategies in LVNC patients since NT-proBNP is a standardized laboratory parameter from a regular blood sample. Based on the present findings in this large LVNC cohort, regular measurement of NT-proBNP may improve risk stratification and influence follow-up intervals in patients with this rare cardiomyopathy.

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FIGURE LEGENDS

Figure 1A: NT-proBNP over time and before an event (death or heart transplantation)

Dot plot charts representing values of NT-proBNP measurements over time except event-preceding measurements (n = 275) in all patients, and event-preceding measurements (n = 15) in patients reaching the endpoint. The horizontal line indicates the median value. The y-axis is depicted in a log2-scale. NT-proBNP = N-terminal fragment of prohormone brain natriuretic peptide.

Figure 1B: Left ventricular ejection fraction over time and before an event (death or heart transplantation)

Dot plot charts representing values of left ventricular ejection fraction measurements over time except event-preceding measurements (n = 513) in all patients and event-preceding measurements (n = 22) in patients reaching the endpoint. The horizontal line indicates the median value.

Figure 1C: Hazard ratios of different parameters in terms of death or heart transplantation

Hazard ratios, adjusted for age and gender, with 95% confidence intervals. HR for every doubling of NT-NT-proBNP, for every 10% decrease in LVEF (age 60 years), for every increase in NYHA functional class, and for every 10% decrease in PoTP (age 60 years). LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; PoTP = percent of target performance; NT-proBNP = N-terminal fragment of prohormone brain natriuretic peptide.

Figure 1D: Hazard ratios of different NT-proBNP and LVEF cut-offs in terms of death or heart transplantation

Hazard ratios, adjusted for age and gender, with 95% confidence intervals depicted on a log10-scale. No events were recorded in patients exhibiting normal NT-proBNP levels, HR not quantifiable (*); HR for NT-proBNP values >2000 ng/l. Only one event was observed in patients with an LVEF >55%, HR not quantifiable (*); HR for LVEF <30%; HR for LVEF <15%. LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal fragment of prohormone brain natriuretic peptide.

Figure 2A: Scatter plot of LVEF and NT-proBNP (log2) measurements

The red points depict the last measurements before death or heart transplantation. The Pearson correlation coefficient is shown in the lower left corner. A regression line is depicted, indicating a moderate to strong negative correlation of NT-proBNP (log2) and LVEF. The plot ignores the grouping of the measurements within the patients. LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal fragment of prohormone brain natriuretic peptide.

Figure 2B: Scatter plot of LVEF and NT-proBNP measurements weighted for length of observation time

The red points depict the last measurements before death or heart transplantation. The area of the circles is proportional to their weight with respect to the length of observation time (maximum observation time has an attributed weight of 1). The weighted Pearson correlation coefficient is shown in the lower left corner. A weighted regression line is depicted. All observations above the line represent increased NT-proBNP values compared to the expected average. The plot ignores the grouping of

the measurements within the patients. LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal fragment of prohormone brain natriuretic peptide.

Figure 2C: Hazard ratios of LVEF and NT-proBNP as combined covariates in terms of death or heart transplantation

Unadjusted and adjusted (for age) hazard ratios with 95% confidence intervals using LVEF and NT-proBNP as covariates simultaneously. HR for every doubling of NT-proBNP and for every 10% decrease in LVEF, indicating a strong influence of NT-proBNP on outcome, whereas LVEF is no longer significant, demonstrating a favourable prognostic power of NT-proBNP. LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal fragment of prohormone brain natriuretic peptide.

Figure 3A: New York Heart Association class distribution over time and before an event (death or heart transplantation)

Distribution of NYHA functional class over time except event-preceding values (n = 420) in all patients and distribution of event-preceding NYHA classes (n = 17) in patients reaching the endpoint. NYHA = New York Heart Association functional class.

Figure 3B: Percent of target performance (PoTP) over time and before an event (death or heart transplantation)

Box plots representing values of PoTP in a bicycle ergometer test over time except event-preceding values (n = 189) in all patients and event-preceding measurements (n = 11) in patients reaching the endpoint. PoTP = percent of target performance.

Figure 1

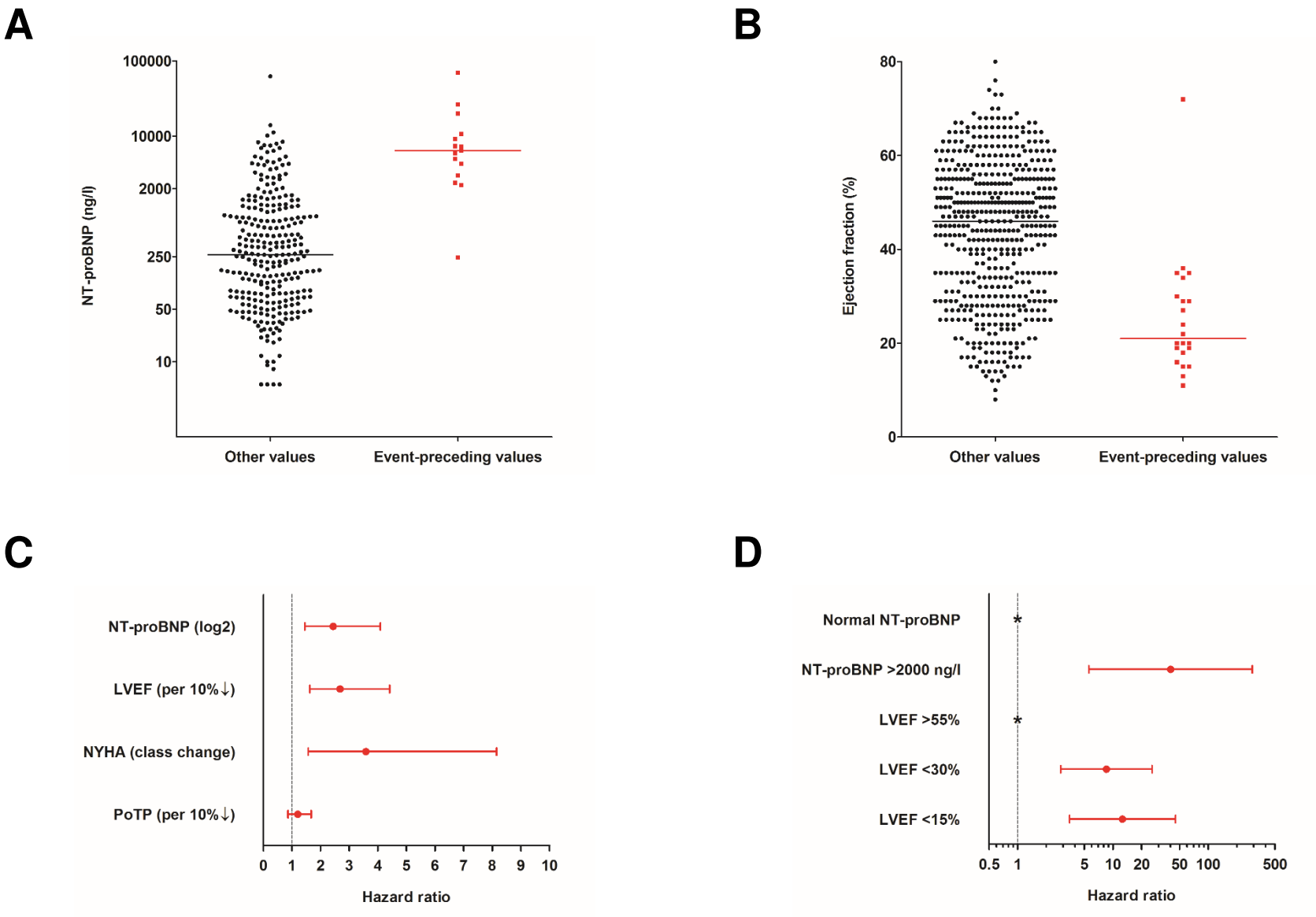
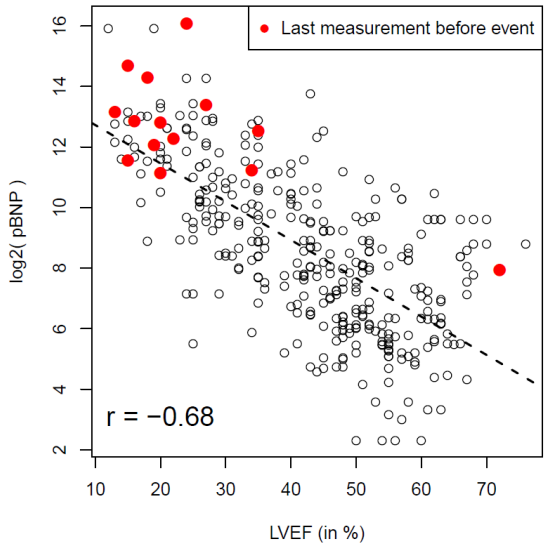
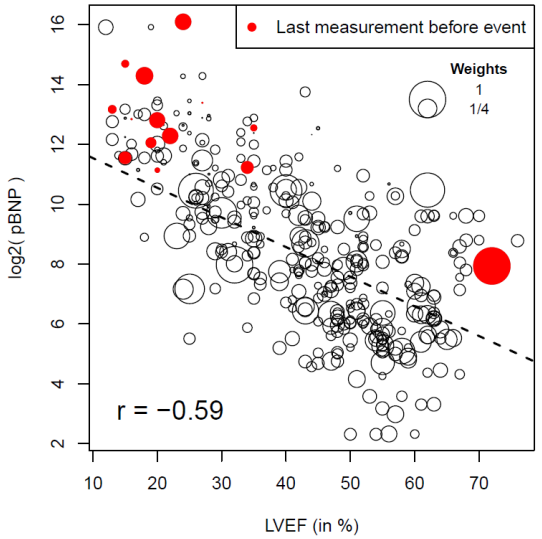

A
100000
10000
2000
250
50
10
NT-proBNP (ng/l)
Other values
Event-preceding values
B
80
60
40
20
0
Ejection fraction (%)
Other values
Event-preceding values
C
NT-proBNP (log2)
LVEF (per 10%↓)
NYHA (class change)
PoTP (per 10%↓)
0 1 2 3 4 5 6 7 8 9 10
Hazard ratio
D
Normal NT-proBNP
NT-proBNP >2000 ng/l
LVEF >55%
LVEF <30%
LVEF <15%
0.5 1 5 10 20 50 100 500
Hazard ratio

Figure 2

A


Last measurement before event
log2(pBNP)
LVEF (in %)
r = −0.68

B


Last measurement before event
Weights
1
1/4
log2(pBNP)
LVEF (in %)
r = −0.59

C

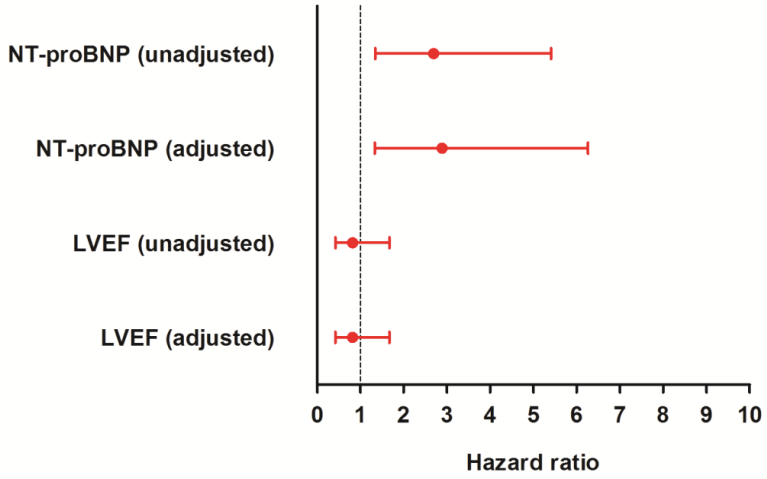
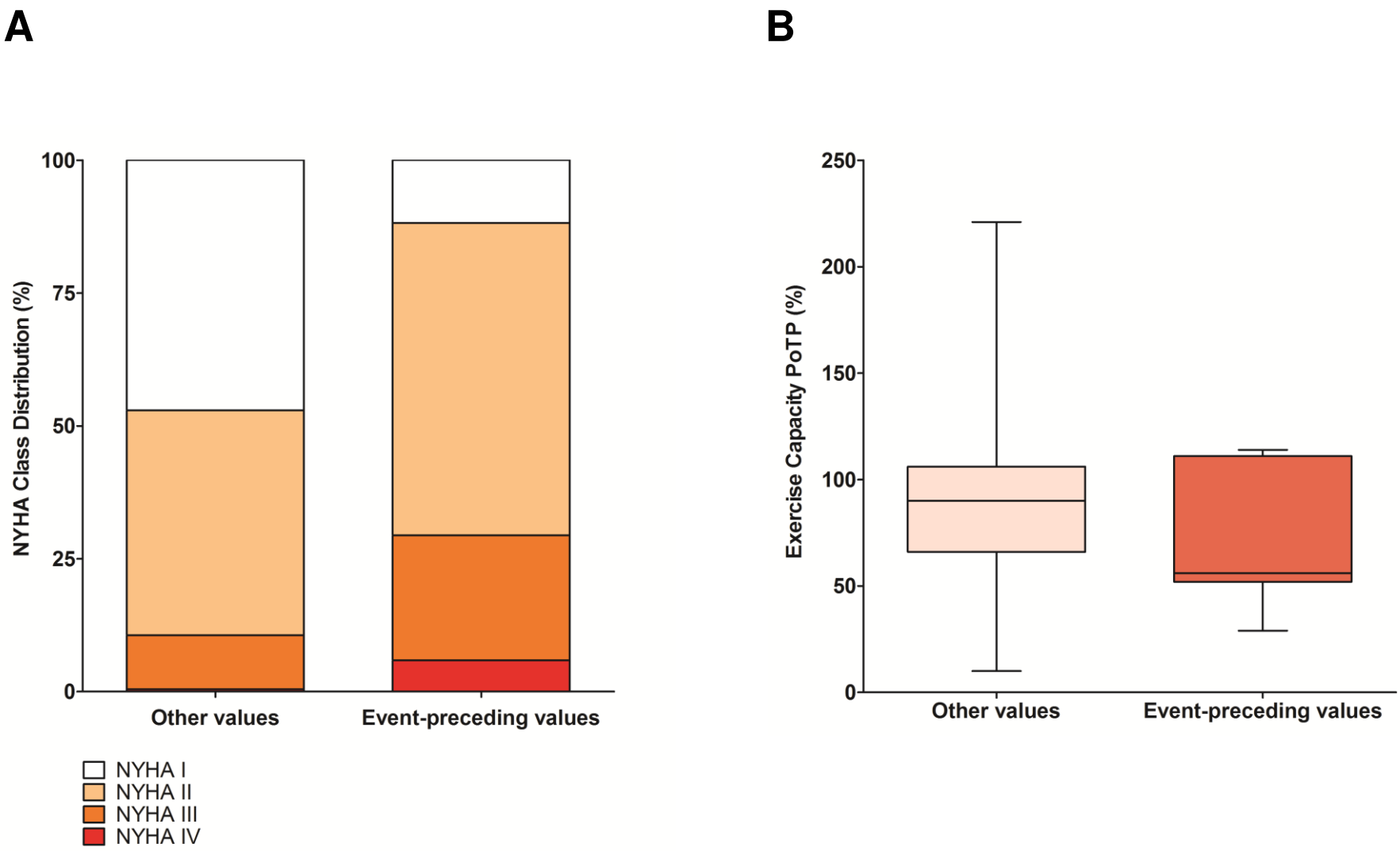

NT-proBNP (unadjusted)
NT-proBNP (adjusted)
LVEF (unadjusted)
LVEF (adjusted)
Hazard ratio

Figure 3


A
B
NYHA Class Distribution (%)
100
75
50
25
0
Other values
Event-preceding values
NYHA I
NYHA II
NYHA III
NYHA IV
Exercise Capacity PoTP (%)
250
200
150
100
50
0
Other values
Event-preceding values